

The predictive value of skin testing in the diagnosis of local anesthetic allergy

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ABSTRACT

Local anesthetics are commonly used medications and can result in adverse reactions. The diagnostic workup of local anesthetic reactions remains controversial. This study was designed to determine the effectiveness of skin testing for local anesthetic allergy evaluation. A retrospective chart review was performed on patients undergoing local anesthetic skin testing. Patients were included if they underwent prick and intradermal skin testing followed by incremental subcutaneous challenge. Charts were further systematically reviewed to evaluate response to local anesthetics in the clinical setting after open subcutaneous challenge. One hundred seventy-eight patients underwent 227 local anesthetic skin tests. Two hundred twenty (97%) of the skin tests were negative. Of the negative skin tests results, 214 (97%) had negative challenge or probable non-IgE-mediated events during challenge. Three patients with six negative skin tests had a local reaction during the open subcutaneous challenge. Seven skin tests on five patients met the criteria for a positive skin test with local anesthetics. One patient had an equivocal local skin reaction with subcutaneous challenge without systemic effects. Three patients had a negative subcutaneous challenge and one patient did not undergo a challenge. Ninety-eight percent of patients receiving local anesthetics in the clinical setting after open subcutaneous challenge tolerated the medications. The negative predictive value of the local anesthetic skin test was 97% with few positive skin tests. Positive local anesthetic skin tests are uncommon and the local anesthetic skin tests have an excellent negative predictive value. Additional study with skin test-only protocols is warranted.

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Local anesthetics are used for many procedures and can result in adverse reactions. A dental series reported an adverse reaction rate as high as 2.5–10% of all patients receiving local anesthetic injections.¹ The majority of these adverse reactions occur *via* nonimmunologic means. Most commonly, these adverse effects are the result of anxiety, psychosomatic responses, excessive dosage, inadvertent injection into the intravascular compartment, and idiosyncratic responses.² IgE-mediated (type I) allergic reactions to local anesthetics are extremely rare and have only been documented in a few case reports.^{3,4}

Although IgE-mediated reactions to local anesthetics are rare, differentiating allergic from nonallergic reactions can be difficult. As a result, patients with adverse reactions to local anesthetics are often referred to allergists. The appropriate workup of patients with a history of adverse reaction to local anesthetic remains controversial. Evaluation may include history only, skin-prick testing, intradermal skin testing, open provocative challenge, or a combination of the all of these.

Numerous studies and case series have evaluated skin testing and open provocative challenges in pa-

tients with a history of local anesthetic reaction.^{5,6} Most of the recent studies have found a low rate of positive skin tests, especially when skin testing/challenging with local anesthetics that are structurally unrelated to the medication suspected of triggering the initial reaction.^{6,7} Reports of positive skin tests followed by negative open provocative challenge exist although these studies often used intradermal skin testing with undiluted or highly concentrated local anesthetic.^{8,9}

At our institution, we typically perform skin-prick tests with undiluted local anesthetic and intradermal skin tests with diluted local anesthetic followed by open challenge. The local anesthetics tested may include the offending agent or an alternative agent. We report one of the largest series of skin tests and challenges to determine the effectiveness of skin testing and open challenges for evaluation of local anesthetic reaction. In addition, further chart review was performed to evaluate patient response to the local anesthetics in the clinical setting after open challenge in the allergist office.

METHODS

A retrospective chart review was performed on all patients undergoing local anesthetic skin testing at our institution during a 16-year period from 1992 to 2008. Approval was obtained from the Mayo Clinic Institutional Review Board and patients declining research authorization were excluded. Patients were included if they underwent the institution's standard local anes-

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thetic protocol. Vital signs and peak flow were obtained at the start of the protocol. Skin-prick testing was performed on the volar surface of the forearm with undiluted preserved local anesthetic solution without epinephrine. The local anesthetic used for testing was chosen by the attending allergist. Some patients had skin testing to the offending agent while others had testing to an alternative agent. The skin test sites were examined after 15 minutes. A positive skin test was defined as a wheal 3×3 mm or greater. Patients with a negative skin-prick test underwent intradermal skin testing.

Intradermal skin tests were also performed on the volar surface of the forearm. A 1:100 dilution of the local anesthetic was injected intradermally to produce an initial wheal of 2×2 mm. Most patients also had histamine (0.1 mg/mL) and a negative control diluent injected intradermally to produce an initial wheal of 2×2 mm. The intradermal skin tests were examined after 15 minutes. A positive intradermal test was defined as a wheal 3 mm greater than the negative control. Patients with negative intradermal skin testing proceeded to open subcutaneous challenge.

Open supervised challenge was performed in the allergy clinic by initially injecting 0.1 mL of undiluted local anesthetic solution subcutaneously into the upper arm. The subcutaneous injection site was examined after 15 minutes. A positive subcutaneous challenge was defined as a wheal 3 mm greater than negative control. If the 0.1-mL challenge was negative, 0.5 mL of undiluted local anesthetic solution was subcutaneously injected into the upper arm at a different location. The subcutaneous injection site was again examined after 15 minutes. If the 0.5-mL challenge was negative, 1.0 mL of undiluted local anesthetic solution was subcutaneously injected into the upper arm at a different location. Vital signs and peak flow were once again obtained before dismissing the patient.

Patient electronic medical records were further surveyed for subsequent local anesthetic administration after the open challenge in the allergy clinic. Clinic and procedure notes were reviewed at the time of the injection to determine if the local anesthetic was tolerated.

RESULTS

Skin Tests Results

One hundred seventy-eight patients underwent 227 local anesthetic skin tests (some patients were tested to multiple anesthetics). Two hundred twenty (97%) of the skin tests were negative. Approximately 60% of local anesthetic skin tests were performed with lidocaine 1 or 2%. The next most commonly tested local anesthetics were bupivacaine 0.5%, procaine 1%, and mepivacaine 1 or 2%. Three patients had positive skin

Table 1 Local anesthetic agents used for skin testing/challenge

Local Anesthetic Agent	No. of Skin Tests Performed	No. of Positive Skin Tests
Lidocaine	140	3
Bupivacaine	35	1
Procaine	28	0
Mepivacaine	24	3

tests with lidocaine and mepivacaine and one patient had a positive skin test with bupivacaine. Two positive skin tests occurred with skin-prick testing and the remaining occurred with intradermal testing (Table 1).

Open Challenge Results

The majority of patients with negative skin tests proceeded to a negative open challenge. Two hundred nine (209/220) of the negative skin tests had a negative open subcutaneous challenge. Five patients with negative skin tests developed nonspecific symptoms without local skin reaction during the challenge. These nonspecific symptoms were not considered a positive challenge based on the study criteria. However, the attending allergist recommended avoidance of the local anesthetic in three of these cases. Six negative skin tests resulted in a local skin reaction (wheal 3 mm greater than control) during subcutaneous open challenge. None of these patients developed systemic symptoms. Based on the criteria described in the Methods section (wheal 3 mm larger than control) these were considered positive challenges; however, the attending allergist interpreted two of these challenges as negative. Overall, six of the negative skin tests (6/220) resulted in positive challenge based on the criteria established for the study. The attending allergist interpreted the challenges slightly differently and considered seven of the negative skin tests (7/220) having a positive challenge (Table 2).

Open challenge results were reviewed on the five patients with positive skin tests. Seven skin tests on five patients (one patient had three positive skin tests) met the criteria of wheal 3 mm larger than control. Patient A underwent no further testing and the attending allergist recommended avoiding the local anesthetic. Patient B had positive skin tests to lidocaine and mepivacaine and did not immediately undergo challenge. Four months later, patient B had negative skin tests and challenge to lidocaine. Patient B also subsequently had a 4×4 mm intradermal wheal with mepivacaine but proceeded to subcutaneous challenge without incident. Patients C and D had positive skin tests with negative challenges. Finally, patient E had a 3×3 mm wheal with intradermal skin testing and

Table 2 Challenge results in patients with negative skin tests ($n = 220$)

	Negative Challenge	Positive Challenge (based on nonspecific symptoms)	Positive Challenge (based on local skin reactions)	Total No. of Positive Challenges
Challenge result based on study criteria*	214	0	6	6/220 (3%)
Challenge result based on attending physician interpretation	213	3	4	7/220 (3%)

*Study criteria of wheal 3 mm greater than negative control.

Table 3 Summary of positive skin test results

Patient	Local Anesthetic	Skin-Prick Test	Intradermal Skin Test	Challenge Result based on Study Criteria	Attending Physician Recommendation
A	Mepivacaine	Negative	Positive	No challenge	Avoid mepivacaine
B	Lidocaine	Positive	Not performed	Negative*	May use lidocaine
B	Mepivacaine	Positive	Not performed	No challenge#	Avoid mepivacaine
B	Mepivacaine	Negative	Positive	Negative	May use mepivacaine
C	Bupivacaine	Negative	Positive	Negative	May use bupivacaine
D	Lidocaine	Negative	Positive	Negative	May use lidocaine
E	Lidocaine	Negative	Positive	Positive§	May use lidocaine

*Challenge not initially performed but 4 mo later had negative skin test and challenge.

#Challenge not initially performed but subsequently had a negative challenge.

§Attending allergist considered challenge to be negative.

subsequently had a 4×4 -mm wheal with the 1 mL subcutaneous challenge without systemic symptoms. The attending allergist noted the challenge to be negative. Thus, one patient (patient E) had an equivocal local skin reaction with subcutaneous challenge without systemic effects, and the remaining four patients had a negative challenge or did not undergo challenge (Table 3).

Postchallenge Experience

Approximately one-half (81/178) of the patients in the study received local anesthetics at our institution after open challenge in the allergy clinic. The local anesthetics were well tolerated with no documented adverse reactions in 98% of the patients. Two patients with positive skin tests and negative or equivocal challenge subsequently received local anesthetics without event. Two patients with negative skin testing and open challenge had adverse reactions after receiving local anesthetic. The first patient developed hives after receiving bupivacaine after negative skin testing and open challenge with lidocaine. The second patient developed flushing and tachycardia after lidocaine with epinephrine administration. Skin testing and challenge with lidocaine were previously negative.

DISCUSSION

The vast majority of skin tests and challenges were negative. Based on the criteria established in the Methods section 97% of skin tests to local anesthetics were negative. Most patients with negative skin testing subsequently had negative open challenge. Many patients went on to receive local anesthetics for necessary procedures without event. The negative predictive value of the local anesthetic skin test when compared with challenge in the allergy clinic or administration for clinical usage was in excess of 97%.

This study is one of the largest to evaluate local anesthetic skin testing and challenges. This series differed from prior studies with regard to the local anesthetics used and the location of the challenges. The patients in this series were tested to alternative local anesthetics in some cases and to the offending agent in some cases. The majority of patients were skin tested using lidocaine, which allowed many of the patients to use lidocaine as opposed to more expensive and less readily available local anesthetics. In addition, the study also reports data from "real-world" challenges. Only two patients reported symptoms in the "real-world" challenges and one of these could potentially be attributed to the coadministration of epinephrine.

The environment and confounding factors may be different in the very controlled allergy clinic challenge compared with the clinical setting. We found that most patients tolerating a local anesthetic challenge in the allergy clinic also tolerated the medication when used for a procedure.

This study has several limitations. The study was retrospective. Many patients were unaware of the details of the original adverse event; so data on the offending agent was not collected. Chart review for post-challenge exposure to the local anesthetics was limited to our clinic. Thus, patients may have subsequently received local anesthetic outside of our institution.

The 2008 "Allergy Diagnostic Testing: An Updated Practice Parameter" states, "Skin testing for diagnosis of local anesthetic allergy is limited by false-positive reactions. The gold standard for establishing a diagnosis of local anesthetic allergy is the provocative challenge."³ The protocol used at our institution extends the recommendations of the Practice Parameter and uses both skin tests and provocative subcutaneous challenge. This method is a safe and effective way for patients with a history of adverse reaction to local anesthetics to receive the medications. In this study, 97% of patients evaluated had a negative challenge and were cleared to receive local anesthetic. The negative predictive value of the skin test was 97%. Based on the excellent negative predictive value and low pretest probability of true local anesthetic allergy, skin testing alone may be sufficient in some cases. Using skin tests only will require further study but may have important implications for the practicing allergist. Local anesthetic challenge can be time-consuming and costly for

the patient and the provider. Many allergy clinics have limited ancillary support and elect not to perform challenges. Skin test-only protocols may allow more patients to be evaluated for local anesthetic allergy and increase the usage of these valuable medications. This study shows that using a protocol incorporating skin testing and provocative challenge is safe and effective and additional study is warranted with skin testing alone protocols.

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